112, second paragraph, as allegedly being indefinite. For the reasons set forth herein, each of the rejections is overcome.

The Invention

The present invention provides RB fusion constructs including fusion polypeptides and vectors encoding them, and methods for the use of such constructs in the treatment of hyperproliferative diseases.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 16-30 and 37 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly being nonenabled. The Office Action alleges that the claims are not enabled for the following reasons: the specification allegedly lacks direction and guidance, there are multiple causes and multiple steps involved in cancer formation, gene delivery in gene therapy is allegedly unpredictable as the result of the viral vector used and the gene encoded, and the specification allegedly does not provide direction or guidance as to how to combine each claimed RB variant with each E2F variant for each specific hyperproliferative disorder. In response, Applicants respectfully traverse the rejection.

The present invention teaches polypeptides and methods for repressing E2F-dependent transcription. These polypeptides and methods are useful for treating hyperproliferative disorders, including cancer. It has been shown that transcriptional repression of genes by RB can be achieved by tethering a pRB to a promoter. For example, GAL4-pRB fusions bind to GAL4 DNA binding domains and repress transcription from p53, Sp-1 or AP-1 elements (*see*, page 1, lines 32-36 of the specification). The polypeptides of the present invention include a fusion of an E2F polypeptide, which is capable of binding a promoter, with an RB polypeptide, which is more efficient in repressing transcription of the E2F-responsive promoter than RB alone (*see*, page 2, lines 11-15 of the specification). According to the present invention, a variety of different forms of RB and E2F polypeptides may be used to treat a

hyperproliferative disorder. One of skill in the art recognizes that the key property of the fusion protein is that it binds to the E2F responsive promoter and inhibits transcription.

To support the rejection, the Examiner has cited a number of references. More particularly, the Examiner has cited Cooper, *Oncogenes*, 1990 ("Cooper"), Feigelson *et al.*, *J. Cell Biochem.*, 1996, 25S:15-22 ("Feigelson *et al.*"), Brandau *et al.*, *Eur. Urol.*, 2001, 39:491-497 ("Brandau *et al.*"), Chellappan, *Mol. Cell. Differ.*, 1994, 2:201-220 ("Chellappan"), Arroyo *et al.*, *Mol. Cell. Biol.*, 1993, 13:6537-6546 ("Arroyo *et al.*"), Dyson, J. *Cell. Sci. Suppl.* 1994, 18-81-87 ("Dyson"), Brechot, *Curr. Opin. Genet. Devel.*, 1993, 3:11-8 ("Dyson"), Reznikoff *et al.*, *Semin. Oncol.*, 1996, 23:571-584, and Carducci *et al.*, *Cancer Treat. Res.*, 1996, 88:219-34 ("Carducci *et al.*") to demonstrate that the development of cancer has multicauses and multisteps (*see*, pages 5-8 of the Office Action). Therefore, according to the Office Action, since the development of cancer involves many causes and steps, treatment of the cancer requires the introduction of genes that are capable of preventing or reversing the steps in the pathophysiology of the disease, and that correction of only one genetic defect in a multistep process of cancer may not be sufficient for cancer treatment (*see*, page 8 of the Office Action).

However, contrary to what is stated in the Office Action, Cooper clearly teaches that introduction of a functional normal Rb gene reverses the tumorigenicity of retinoblastoma cell lines in which the endogenous gene had been deleted (*see*, page 133, lines 17-19 of Cooper). Retinoblastoma cell lines originate from cancer, which, according to the Office Action, developed as a result of many causes involving many steps. Yet, according to Cooper, the Rb gene alone is sufficient to reverse the tumorigenicity of the cancer cells (*see*, page 133, lines 17-19 of Cooper). Furthermore, since the publication of Cooper, it has been discovered and is well-known in the art that Rb functions, among other things, to regulate the activity of transcription factors (*e.g.*, E2F family members) which, in turn, controls transcription of a number of cell cycle regulatory genes (*e.g.*, cyclin E and cdk2). Therefore, according to Cooper, the

introduction of Rb obviously affects the activity of more than one protein. In fact, it is well know in the art that cell cycle regulatory genes play pivotal roles during the development of cancer. Thus, contrary to what is stated in the Office Action, the introduction of Rb would be useful to treat hyperproliferative disorders, including cancer, since its effect is widespread. Furthermore, the present invention teaches fusion polypeptides comprising a fusion of an E2F polypeptide with an RB polypeptide that are more efficient in repressing transcription of the E2F-dependent genes than RB alone (*see*, page 2, lines 11-15 of the specification). As such, Applicants respectfully request that the enablement rejection be withdrawn.

According to the Office Action, Chellappan teaches that E2F exists in complexes with different cellular proteins such as the retinoblastoma tumor suppressor protein, p107, p130, cyclins A and E, and kinase cdk2 (*see*, page 5 of the Office Action). It appears that the Examiner is concerned that the specification does not teach which hyperproliferative disease involve a functional cyclin A binding domain (*see*, page 6 of the Office Action). However, in the present invention, the purpose of the E2F polypeptide in the fusion polypeptide is simply to provide the E2F DNA binding portion in order to tether the fusion polypeptide to the DNA. Therefore, the presence of a functional cyclin A binding domain is not critical to the activity of the fusion polypeptide (*see*, page 7, lines 2-6 of the specification). Clearly, the fusion polypeptide of the present invention will function properly whether or not a functional cyclin A binding domain is present. As such, Applicants respectfully request that the enablement rejection be withdrawn.

According to the Office Action, there is no teaching or guidance in the specification as to which specific vector should be used for delivering DNA or polypeptide to any specific target cells for any specific disorder. In response, Applicants assert that the compositions and methods of the present invention are broadly applicable to a number of different target cells for a number of different hyperproliferative disorders. There is ample teaching in the specification which guides one of skill in the art to devise

vectors of the present invention without undue experimentation. For example, a description of the desirable components of the vector is described on page 9, lines 13-28 of the specification. Promoters useful in the present invention are discussed on page 9, lines 29-38 and page 10, lines 1-13 of the specification. In addition, numerous examples of a number of suitable promoters are given on page 10, lines 14-36 and on pages 11-12 of the specification. One of skill in the art is familiar with commonly used molecular biology techniques useful for constructing vectors of the present invention following the guidelines provided in the specification. As such, Applicants respectfully request that the Examiner withdraw the rejection.

On page 9 of the Office Action, the Examiner notes that human gene therapy is unpredictable. The rejection is not apparently based on an assertion that any particular procedure required to practice the claimed methods is unpredictable or even difficult to carry out. For example, Applicants do not understand the rejection to be based on an allegation that construction of recombinant vectors encoding RB and RB-E2F fusion proteins, preparation of delivery vehicles (viral vectors, lipids, and the like) or the preparation and administration of pharmaceutical compositions containing the delivery vehicles is unpredictable. Rather, the rejection is based on a concern that, if one of skill carries out these steps a ***useful result*** (*e.g.*, suppression of tumorigenicity of a cancer cell) will not be obtained.

As explained in MPEP §2107(d), a close relationship exists between 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph. In particular, the MPEP states:

> ***[T]he Federal Circuit recently noted, "[o]bviously, if a claimed invention does not have utility, the specification cannot enable one to use it." In re Brana, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995). As such,*** a rejection properly imposed under 35 U.S.C. 101 should be accompanied with a rejection under 35 U.S.C. 112, first paragraph. ***It is equally clear that a rejection based on "lack of utility," whether grounded upon 35 U.S.C. 101 or 35 U.S.C. 112, first paragraph, rests on the same basis***

> ***(i.e., the asserted utility is not credible)***. MPEP §2107(d). [Emphasis added]

Thus, Applicants understand the rejection to be an argument that because gene therapy is "unpredictable", claimed methods that cover such therapies lack a credible utility under the patent laws. As a result, according to the Examiner, such claims are not enabled under §112, first paragraph, because undue experimentation would allegedly be required to achieve a useful result. This logic apparently applies to all the claims, even claims directed to exemplified embodiments. As explained below, the underlying conclusion that gene therapy is too unpredictable to achieve a useful result, as defined by the patent laws, is incorrect.

Applicants liken their situation to one who has invented a novel chemical process: while commercially profitable operation of the process would be desirable, the inventor need not demonstrate that his process would be profitable in order to secure a patent. Similarly, while therapeutic inhibition is a desirable goal of the invention, applicants need not demonstrate that their method would be ***clinically*** practical in order to secure patent protection. Applicants therefore submit that general references teaching the clinical difficulties of human gene therapy are inapposite to their claims. As Applicants have taught a specific method of treating a hyperproliferative disorder, the burden is on the Examiner to come forth with evidence or reasoning, not merely assertions, why one of skill in the art could not use the invention's teachings to actually treat a hyperproliferative disorder *in vivo*.

Moreover, the fact that Applicants have not taught solutions to all the problems posed by human gene therapy is irrelevant. An Applicant is not required to solve all the technical problems inherent in his field, so long as he has taught how to practice the claimed invention without undue effort. As the late Judge Rich explained:

> [Applicants] are thus, it seems to us somewhat in the portion of a suspension-bridge builder who has discovered that maintaining certain relationships between the height above the roadway of the main piers and the distance

> between the piers will result in bridges of substantially increased strength. Disclosure by the bridge builder of this relationship would certainly not solve all the time-consuming problems of bridge designing or building, but it would, we think, enable any person skilled in the art to practice the invention.

In re Cook, 439 F.2d 730, 732-3 (C.C.P.A. 1971). Likewise, while Applicants did not solve all the problems of practical gene therapy, they are entitled to claim their advance unless the Examiner demonstrates that the invention would be wholly inoperative as claimed.

In conclusion, the Examiner has not met the burden of providing acceptable objective evidence or reasoning that calls into question the general applicability of gene therapy for the purposes of patentability. In the Office Action, the Examiner relies on selected references to argue that gene therapy is unworkable. The weight of the evidence, when considered as a whole, indicates that those of skill in the art consider gene therapy to be "feasible" and have invested considerable resources to its development. Analyzed under the proper standards for evaluating the utility and/or enablement of therapeutic methods, the claims fully comply with §112, first paragraph. Therefore, Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph, be withdrawn.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 17 and 34-36 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. According to the Office Action, claims 17 and 34-36 do not provide further limitation to claims 16 because a different product is administered. In response, Applicants respectfully traverse the rejection.

The present invention teaches compositions and methods for treating a hyperproliferative disorder. The method of claim 16 of the present invention comprises administering an effective dose of a fusion polypeptide that comprises a transcription factor and a functional growth suppression domain of a retinoblastoma polypeptide. One

of the ways in which such a dose may be administered is, for example, by administration of nucleic acids encoding the fusion polypeptide. Claim 17 states the following:

> 17. (Amended) The method of claim 16, wherein the fusion protein is encoded by a nucleic acid delivered to the patient.

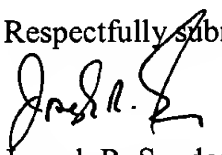
Clearly, claim 17 relates to a method of treating a hyperproliferative disorder comprising administering an effective dose of a fusion polypeptide that comprises a transcription factor and a functional growth suppression domain of a retinoblastoma polypeptide. Claim 17 further limits claim 16 in that it specifies that the polypeptide is administered by delivering a nucleic acid encoding the fusion protein to the patient. Contrary to what is stated in the Office Action, a different product is ***not*** administered in claim 17 than 16. The product administered in claim 16 may, in fact, include a nucleic acid. Claims 34 and 36 are dependent upon claim 17 and therefore, also clearly provide further limitation to claim 16. As such, Applicants respectfully request that the rejection under 35 U.S.C. § 112, second paragraph be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at .

Respectfully submitted,



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